Why a powerful cancer drug only helps some patients

A new type of drug that unleashes the immune system on tumors has been a remarkable success, but only for some cancer patients. Now researchers have found a genetic signature within lung tumors that seems to predict whether this immunotherapy drug will work—and who will benefit most.

Tumor cells can hide from the immune system by activating a receptor, called PD-1, on the surface of the immune cells known as T cells. Instead of attacking the tumor cells, the T cells leave them alone. The new drug is an antibody that inhibits PD-1, blocking this "checkpoint" and freeing the T cells to wipe out the tumor cells. In clinical trials, PD-1 blockers and other checkpoint inhibitors have extended the lives of patients with several cancer types for years, far longer than conventional treatments. The U.S. Food and Drug Administration has approved several of these drugs for melanoma and one of them, nivolumab, became the first to win approval for lung cancer last week. But checkpoint inhibitors work only for some people—PD-1 inhibitors shrink tumors in about 20% to 30% of lung cancer patients—and researchers are scrambling to figure out why.

One hypothesis is that checkpoint inhibitors are more likely to work on tumors that have more mutations. These mutations are not necessarily those that allow tumor cells to divide uncontrollably or spread to other places; instead, they may simply encode abnormal proteins that do nothing for the cancer cell. But they can matter for immunotherapies because the aberrant molecules may act as antigens—foreign molecules in the body that trigger an immune response. The more mutations in a patient's tumor, the more of these so-called neoantigens, and hence a stronger response from T cells in patients taking a checkpoint inhibitor, the thinking goes.

Some recent studies support this view. Melanoma patients with more neoantigen-coding mutations in their tumors, for example, were more likely to respond to a

checkpoint inhibitor that blocks a protein called CTLA-4.

Now, the same seems to hold true for lung cancer. Timothy Chan of Memorial Sloan Kettering Cancer Center in New York City, who led the melanoma study, and co-workers sequenced the exome—the protein-coding DNA—of tumors from 34 people with non-small cell lung cancer who had been treated with a PD-1 inhibitor called pembrolizumab. They found that patients were much more likely to respond to the drug if their tumor had more of the type of mutation that results in an altered protein. For example, 13 of 18 (72%) patients with at least 178 mutations responded for 6 months or longer, compared with one of 13 (8%) of those with fewer mutations. Moreover, the 16 lung cancer patients who had a distinctive pattern of mutations caused by smoking were more likely to respond than the presumed nonsmokers, who had fewer, different mutations, Chan's group reports online today in *Science*.

The correlation between mutations and therapeutic response to the cancer drugs is "eye-popping," says cancer researcher Drew Pardoll of Johns Hopkins University School of Medicine in Baltimore, Maryland, who was not involved with the study but has collaborated with Chan's group. "It's a very important result." Although the results don't necessarily mean that all nonsmokers won't respond to PD-1 blockers, sequencing the DNA of tumor biopsies could help oncologists decide which drug to give first, he and Chan say. And it suggests these drugs may work on other smoking-related cancers, such as esophageal and head and neck cancers, Chan adds.

Researchers are also exploring the possibility of giving patients a personalized vaccine made from the neoantigens in their tumor to bolster their response to a checkpoint inhibitor. "I think the potential here is enormous," says Roy Herbst, a lung cancer researcher at Yale University.